



Meeting Report: Consensus Statement— Parkinson's Disease and the Environment: Collaborative on Health and the Environment and Parkinson's Action Network (CHE PAN) Conference 26–28 June 2007.

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Meeting Report: Consensus Statement—Parkinson's Disease and the Environment: Collaborative on Health and the Environment and Parkinson's Action Network (CHE PAN) Conference 26–28 June 2007

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BACKGROUND: Parkinson's disease (PD) is the second most common neurodegenerative disorder. People with PD, their families, scientists, health care providers, and the general public are increasingly interested in identifying environmental contributors to PD risk.

METHODS: In June 2007, a multidisciplinary group of experts gathered in Sunnyvale, California, USA, to assess what is known about the contribution of environmental factors to PD.

RESULTS: We describe the conclusions around which they came to consensus with respect to environmental contributors to PD risk. We conclude with a brief summary of research needs.

CONCLUSIONS: PD is a complex disorder, and multiple different pathogenic pathways and mechanisms can ultimately lead to PD. Within the individual there are many determinants of PD risk, and within populations, the causes of PD are heterogeneous. Although rare recognized genetic mutations are sufficient to cause PD, these account for < 10% of PD in the U.S. population, and incomplete penetrance suggests that environmental factors may be involved. Indeed, interplay among environmental factors and genetic makeup likely influences the risk of developing PD. There is a need for further understanding of how risk factors interact, and studying PD is likely to increase understanding of other neurodegenerative disorders.

KEY WORDS: cholesterol, coffee, dairy products, diet, dopamine, fatty acids, metals, nonsteroidal anti-inflammatory drugs, Parkinson's disease, pesticides, polychlorinated biphenyls, smoking, statins, urate. *Environ Health Perspect* 117:117–121 (2009). doi:10.1289/ehp.11702 available via <http://dx.doi.org/> [Online 26 August 2008]

Parkinson's disease (PD) is the second most common neurodegenerative disorder. The likelihood of developing PD increases with age. PD is rare before age 50. The average age of onset is in the mid- to late 60s (Bower et al. 1999; de Rijk et al. 1995; Marras and Tanner 2002; Van den Eeden et al. 2003). As the U.S. population ages, prevalence of this disabling disorder is expected to rise dramatically (Dorsey et al. 2007). Unfortunately, few valid data that address changes in PD incidence or prevalence over time are available. In fact, active case-finding efforts in communities detect as many as 10–40% of cases of PD for the first time, suggesting that underestimation of PD prevalence is common (de Pedro-Cuesta 1991; de Rijk et al. 1997).

The symptoms of PD are slowly progressive. Well-recognized clinical features of PD are slowed movements, tremor, rigidity, and difficulties with gait and balance. However,

other features commonly occur, including changes in olfaction, autonomic function, cognitive function, affect, sleep, and energy level (Alves et al. 2005; Burn et al. 2006; Pfeiffer 1998; Stern et al. 1994).

In PD, specific neuronal populations degenerate. Neurodegeneration occurs in concert with the deposition of aggregates of the protein alpha synuclein in neuronal cell bodies and processes (Spillantini et al. 1998). The classical focus has been on dopamine-releasing cells in the substantia nigra, because dopamine replacement can partially correct some of the motor features of PD. It has long been known, however, that many other neuronal populations are also affected in PD. Recently, converging epidemiologic and pathologic data suggest that years or even decades before the onset of these classical features of PD, neurons outside of the central nervous system may be injured (Abbott et al. 2005, 2007; Braak et al. 2004;

Langston 2006; Ross et al. 2008). If this is correct, current concepts of PD will need revision. Clarification may provide exciting new opportunities for treatment and intervention.

In the 1980s, the observation that intravenous exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) caused parkinsonism in humans offered important insights into environmental triggers (Langston et al. 1983). Even though relatively uncommon genetic mutations are sufficient to cause

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some cases of PD, twin studies conclude that the contribution of genetic makeup to the risk of most cases of PD is limited (Tanner et al. 1999; Wirdefeldt et al. 2004). Moreover, studies of uncommon genetic forms of PD have shown that changes in the structure of proteins that can lead to neural dysfunction, and death can also be caused independently by some environmental toxicants (Lee 2003; Purisai et al. 2005; Uversky et al. 2001; Vila et al. 2000). As a result, a general view has evolved that the vast majority of cases of PD are caused by environmental factors interacting with genetic makeup.

People with PD, their families, scientists, health care providers, and the general public are increasingly interested in identifying environmental contributors to PD with an eye toward not only more effective treatments but also prevention. What percentage of cases involves preventable causes? What precautionary interventions would be warranted and effective, and when must they be implemented? Can individuals destined to develop neurologic dysfunction due to PD be identified before typical motor symptoms manifest?

The current scientific literature does not provide conclusive answers to most of these and other relevant questions. But indications from epidemiology, basic neurobiology, and toxicology increasingly support the conclusion that a large portion of the risk of developing PD may be attributable to environmental exposures. Therefore, the risk of PD is theoretically reducible to the extent that some cases may be preventable.

Purpose of Conference

Responding to these questions and concerns, a multidisciplinary group of experts gathered in Sunnyvale, California, USA, 26–28 June 2007, to assess what is known about the contribution of environmental factors to PD. Participants included toxicologists, epidemiologists, geneticists, neuroscientists, and medical practitioners. They were joined by representatives of PD advocacy groups and people with PD to review the state of environmental health science as it pertains to PD.

The purposes of the meeting were as follows:

- To review findings from diverse research disciplines concerning environmental factors that alone or in combination with genetic variables provide a biologic basis of PD
- To identify conclusions that could be drawn with confidence from existing data
- To identify plausible but uncertain conclusions
- To identify research gaps and needs and to describe features of a coherent research agenda.

Participants recognized the existence of various syndromes that may share some clinical and neurobiologic features with classic PD.

Sometimes the term “parkinsonism” is used to refer to these syndromes. They often involve more extensive (or less specific) brain injury than is typically seen in classic PD and can be degenerative or nondegenerative (e.g., carbon monoxide-induced parkinsonism, carbon tetrachloride-induced parkinsonism, vascular parkinsonism). However, boundaries between PD and parkinsonism are evolving concepts. For this reason, participants were not asked to discuss and come to a consensus definition of PD.

Participants did not attempt to rank specific pathogenic mechanisms with respect to their relative importance in PD causation. Nonetheless, various combinations of alpha synuclein deposition, mitochondrial dysfunction, proteasome dysfunction, oxidative stress, and inflammation arose in discussions of potential contributors in causal pathways.

Participants were also not asked to address and did not consider *a*) an exhaustive list of toxicants that have been associated with PD (examples of toxicants not considered include organic solvents, electromagnetic fields); or *b*) factors that may influence the progression of PD (as differentiated from causes of onset of PD).

Over the course of the meeting, the following core points of consensus were identified, which we offer in this summary to acquaint scientists, medical professionals, public health advocates, and policy makers with the current state of understanding in the field, as seen by conference participants, and to help in identifying fruitful research strategies.

Findings

Sufficient evidence of a causal relationship. Based on existing evidence, we are confident of the following:

- PD is a complex disorder, and multiple different pathogenic pathways and mechanisms can ultimately lead to PD. Within the individual there are multiple determinants of PD risk, and within populations the causes of PD are heterogeneous. The interplay among environmental factors and genetic makeup likely influences the risk of developing PD (Chade et al. 2006; Warner and Schapira 2003).
- PD risk increases with age (Bower et al. 1999; de Rijk et al. 1995; Van den Eeden et al. 2003; Zhang et al. 2003).
- Studying PD is likely to increase understanding of other neurodegenerative disorders.
- Rare recognized genetic mutations are sufficient to cause PD (Singleton et al. 2003; Warner and Schapira 2003). However, collectively these genetic mutations account for < 10% of PD in the U.S. population. Moreover, even in these rare instances, incomplete penetrance suggests that environmental factors may be involved (Elbaz 2008).

- In addition to rare genetic mutations, PD or parkinsonism can also rarely be induced primarily by exposure to toxicants that directly target the area of the brain involved in PD. MPTP is an example of such a toxicant (Langston et al. 1983).

PD risk factors are categorized according to the terminology of the Institute of Medicine (IOM) for strength of evidence. IOM committees sometimes classify the evidence of association between exposure to a specific agent and a specific health outcome into five previously established categories, as set forth below. The group of experts gathered in Sunnyvale decided to use these categories as a means of describing their evaluation of the state of the evidence with respect to the influence of various factors on PD risk. Criteria for inclusion in each category are described at the outset.

Participants felt that these categories for describing the strength of evidence pertaining to individual risk factors were useful even though not based here on a systematic evidence-based literature review. Risk factors were assigned to the various categories based on consensus opinion of those attending the conference. Moreover, within each category there is no attempt to list the entries in any particular order.

Sufficient evidence of an association. In this IOM category, evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

- Men are at greater risk of PD than women (Bower et al. 1999; de Rijk et al. 1995; Van den Eeden et al. 2003). However, increased risk to a disease can occur because of inherently increased susceptibility, increased exposures to causal agent(s), or combinations of the two (Wooten et al. 2004). Current evidence is not sufficient to explain with confidence the increased risk in males.
- Evidence is sufficient to conclude with confidence that cigarette smokers have a lower risk of PD than nonsmokers (Hernan et al. 2002; Ritz et al. 2007). PD risk may also be lower for people who use other tobacco products, although the evidence is not as extensive or persuasive as for cigarette smokers, and conference participants were less confident in drawing conclusions.
- Evidence is also sufficient to conclude that male coffee drinkers have a lower risk of PD than females (Ascherio et al. 2004; Ross

et al. 2000). For women coffee drinkers and people consuming other caffeinated beverages, evidence is limited, but a similar pattern seems to emerge (Ascherio et al. 2001).

Conference participants are confident of the associations but uncertain about the causal relationships or pathways by which smoking and coffee consumption might have a neuroprotective effect. Various biologic mechanisms have been proposed. For example, nicotine in cigarettes and caffeine in coffee are hypothesized to be agents that may confer a lower PD risk. However, noncausal explanations for these associations are also plausible (Hernan et al. 2002), uncertainties remain, and no consensus has been achieved. Nonetheless, further investigation into the biologic mechanisms by which female sex, cigarette smoking, and coffee consumption lower PD risk is warranted and may result in important insights into the etiology and progression of PD.

Limited suggestive evidence of an association. In this IOM category, evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding. Alternatively, several studies of less quality show consistent positive associations, and the results are probably not due to bias, including confounding.

Available scientific studies suggest an association between a number of different factors and PD risk. Here, the data are limited but tend to point toward a valid association with PD risk. Causal mechanisms explaining the associations, if they exist, are not well understood.

- People with higher levels of physical activity have a reduced risk of PD (Thacker et al. 2008).
- Men, and possibly women, with higher blood urate levels have a reduced risk of PD (Davis et al. 1996; Weisskopf et al. 2007).
- People taking nonsteroidal anti-inflammatory drugs have a lower risk of PD (Powers et al. 2008a; Wahner et al. 2007).
- Men with high dietary intake of dairy products have an increased risk of PD (Chen et al. 2002; Park et al. 2005).
- Farmers and agricultural workers have an increased risk of PD (Hertzman et al. 1994; Gorell et al. 1998; Tuchsien and Jensen 2000). Epidemiologic studies often classify study participants according to their occupation and examine for associations between occupations and outcomes of interest. In these cases, inferences about potential

exposures that characterize those occupations may be drawn, but they remain as inferences and should not be confused with estimates of exposure to specific environmental agents.

- People exposed to pesticides have an increased risk of PD (Dick et al. 2007; Gorell et al. 1998; Hancock et al. 2008; Kamel et al. 2007). However, epidemiologic study designs may classify study participants according to reported exposures to classes of chemicals or other agents. In these cases, associations between the class of environmental agents and outcome of interest may be identified, but in most cases specific agents that account for the association cannot be further identified from those data. Meeting participants note the evidence suggesting a direct association between pesticide exposure and PD risk but are unable to draw any conclusions about specific agents that may be responsible.
- People with traumatic brain injury have an increased risk of PD (Bower et al. 2003; Dick et al. 2007; Goldman et al. 2006).
- Certain variants of genes can modify the risk of PD. The risk may be higher or lower depending on the variant (Warner and Schapira 2003).

Inadequate/insufficient evidence to determine whether an association exists. In this IOM category, evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

- People with higher dietary intake of polyunsaturated fatty acids have lower risk of PD (de Lau et al. 2005).
- People with higher blood cholesterol have lower risk of PD (Hu et al. 2008; Simon et al. 2007).
- Dietary sources of urate lower the risk of PD (Annamaki et al. 2007; Gao et al. 2008).
- People taking statins are at lower risk of PD (Becker et al. 2008; Wahner et al. 2008).
- Postmenopausal women taking exogenous estrogen are at reduced risk of PD (Currie et al. 2004; Popat et al. 2005).
- People with increased body mass index or body fat are at increased risk of PD (Hu et al. 2006; Logroscino et al. 2007).
- Women occupationally exposed to polychlorinated biphenyls (electrical capacitance workers) are at increased risk of PD (Prince et al. 2006; Steenland et al. 2006).
- People with higher educational level are at higher risk of PD (Frigerio et al. 2005).
- People exposed to some specific pesticides have an increased risk of PD (paraquat, maneb, dieldrin) (Dick 2006; Drechsel and Patel 2008; Kamel et al. 2007). *In vitro* and *in vivo* laboratory animal studies of some specific pesticides (e.g., rotenone, paraquat,

maneb) demonstrate toxicity to nigral dopaminergic neurons and reveal biologic mechanisms by which exposure to those pesticides is plausibly linked to PD risk (Thiruchelvam et al. 2000; Uversky 2004).

- People exposed to some heavy metals have an increased risk of PD (Gorell et al. 1998; Mergler et al. 1994).

Limited suggestive evidence of no association. In this IOM category, evidence from available studies is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure studied cannot be excluded.

Welding is not associated with risk of PD (Marsh and Gula 2006; Santamaria et al. 2007).

Consensus not reached on category of association. In this IOM category, if the entire committee did not agree on a conclusion, then the association was not assigned a category.

- People living in rural areas have/do not have (Kuopio et al. 1999; Priyadarshi et al. 2001) an increased risk of PD.
- Vitamin E, vitamin C, and carotenoids are/are not associated with PD risk (Etminan et al. 2005; Zhang et al. 2002).
- Dietary saturated fats are/are not associated with risk of PD (de Lau et al. 2005; Gao et al. 2007; Powers et al. 2008b).
- Well water drinking is/is not associated with PD risk (Kuopio et al. 1999; Priyadarshi et al. 2001).
- Race/ethnicity is/is not associated with PD risk (Mayeux et al. 1995; Van den Eeden et al. 2003; Zhang and Román 1993).

Research Needs

- Well-designed case-control studies with sufficient power are needed—perhaps through consortia or multicenter—as well as strict attention to bias and confounding.
- Consider the question of appropriate control groups. Consider alternatives to traditional sources of controls used in the past such as random digit dialing and centers for Medicare and Medicaid services, as these sources are now often impractical because of privacy and other considerations.
- PD registries, particularly inclusive, legally mandated, population-based registries, are essential to description of demographic, geographic, and temporal patterns and trends.
- Diagnostic criteria for cases need to be well defined in studies. Criteria and disease definition may vary depending on the specific hypothesis being tested. Similarly, characterization of clinical features is critical. Some risk factors may be specific for classic PD,

whereas others may be common for all types of parkinsonism.

- Biomarkers of disease are needed, beginning with early stages.
- More consistent attempts are needed to look at both susceptibility genes and environmental agents in combination.
- Better measures of the exposures of interest are needed.

Research Questions

In addition to known risk factors for PD, conference participants identified a number of others in need of further investigation. Even for those that are well established, however, there is a need for additional information about mechanisms by which they influence PD risk. Moreover, in addition to individual risk factors, conference participants recognized a need for further understanding of how risk factors interact as they contribute to the multiple pathogenic pathways that may ultimately result in PD.

REFERENCES

- Abbott RD, Ross GW, Petrovitch H, Tanner CM, Davis DG, Masaki KH, et al. 2007. Bowel movement frequency in late-life and incidental Lewy bodies. *Mov Disord* 22(11):1581–1586.
- Abbott RD, Ross GW, White LR, Tanner CM, Masaki KH, Nelson JS, et al. 2005. Excessive daytime sleepiness and subsequent development of Parkinson disease. *Neurology* 65(9):1442–1446.
- Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. 2005. Progression of motor impairment and disability in Parkinson disease: a population-based study. *Neurology* 65(9):1436–1441.
- Annamaki T, Muuronen A, Murros K. 2007. Low plasma uric acid level in Parkinson's disease. *Mov Disord* 22(8):1133–1137.
- Ascherio A, Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Rodriguez C, et al. 2004. Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort: the modifying effects of estrogen. *Am J Epidemiol* 160(10):977–984.
- Ascherio A, Zhang SM, Hernán MA, Kawachi I, Colditz GA, Speizer FE, et al. 2001. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. *Ann Neurol* 50(1):56–63.
- Becker C, Jick SS, Meier CR. 2008. Use of statins and the risk of Parkinson's disease: a retrospective case-control study in the UK. *Drug Saf* 31(5):399–407.
- Bower JH, Maraganore DM, McDonnell SK, Rocca WA. 1999. Incidence and distribution of parkinsonism in Olmsted County, Minnesota, 1976–1990. *Neurology* 52:1214–1220.
- Bower JH, Maraganore DM, Peterson BJ, McDonnell SK, Ahlskog JE, Rocca WA. 2003. Head trauma preceding PD: a case-control study. *Neurology* 60(10):1610–1615.
- Braak H, Ghebremedhin E, Rub U, Braatzke H, Del Tredici K. 2004. Stages in the development of Parkinson's disease—related pathology. *Cell Tissue Res* 318(1):121–134.
- Burn DJ, Rowan EN, Allan LM, Molloy S, O'Brien JT, McKeith IG. 2006. Motor subtype and cognitive decline in Parkinson's disease, Parkinson's disease with dementia, and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry* 77(5):585–589.
- Chade AR, Kasten M, Tanner CM. 2006. Nongenetic causes of Parkinson's disease. *J Neural Transm* 113(suppl):147–151.
- Chen H, Zhang S, Hernan M, Willett W, Ascherio A. 2002. Diet and Parkinson's disease: a potential role of dairy products in men. *Ann Neurol* 52:793–801.
- Currie LJ, Harrison MB, Trugman JM, Bennett JP, Wooten GF. 2004. Postmenopausal estrogen use affects risk for Parkinson disease. *Arch Neurol* 61(6):886–888.
- Davis JW, Grandinetti A, Waslien CI, Ross GW, White LR, Morens DM. 1996. Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. *Am J Epidemiol* 144(5):480–484.
- de Lau LM, Bornebroek M, Witterman JC, Hofman A, Koudstaal PJ, Breteler MM. 2005. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. *Neurology* 64(12):2040–2045.
- de Pedro-Cuesta J. 1991. Parkinson's disease occurrence in Europe. *Acta Neurol Scand* 84(4):357–365.
- de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meché FG, et al. 1995. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. *Neurology* 45(12):2143–2146.
- de Rijk MC, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S. 1997. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 62(1):10–15.
- Dick FD. 2006. Parkinson's disease and pesticide exposures. *Br Med Bull* 79–80:219–231.
- Dick FD, De Palma G, Ahmadi A, Scott NW, Prescott GJ, Bennett J, et al. 2007. Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occup Environ Med* 64(10):666–672.
- Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. 2007. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 68(5):384–386.
- Drechsel DA, Patel M. 2008. Role of reactive oxygen species in the neurotoxicity of environmental agents implicated in Parkinson's disease. *Free Radic Biol Med* 1:44(11):1873–1886.
- Elbaz A. 2008. LRRK2: bridging the gap between sporadic and hereditary Parkinson's disease. *Lancet Neurol* 7(7):562–564.
- Eminan M, Gill SS, Samii A. 2005. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. *Lancet Neurol* 4(6):362–365.
- Frigerio R, Elbaz A, Sanft KR, Peterson BJ, Bower JH, Ahlskog JE, et al. 2005. Education and occupations preceding Parkinson disease: a population-based case-control study. *Neurology* 65(10):1575–1583.
- Gao X, Chen H, Choi HK, Curhan G, Schwarzschild MA, Ascherio A. 2008. Diet, urate, and Parkinson's disease risk in men. *Am J Epidemiol* 167(7):831–838.
- Gao X, Chen H, Fung TT, Logroscino G, Schwarzschild MA, Hu FB, et al. 2007. Prospective study of dietary pattern and risk of Parkinson disease. *Am J Clin Nutr* 86(5):1486–1494.
- Goldman SM, Tanner CM, Oakes D, Bhudhikanok GS, Gupta A, Langston JW. 2006. Head injury and Parkinson's disease risk in twins. *Ann Neurol* 60(1):65–72.
- Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. 1998. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. *Neurology* 50:1346–1350.
- Hancock DB, Martin ER, Mayhew GM, Stajich JM, Jewett R, Stacy MA, et al. 2008. Pesticide exposure and risk of Parkinson's disease: a family-based case-control study. *BMC Neurol* 8:6.
- Hernan MA, Takkouche B, Caamanolsoma F, Gestel-Otero J. 2002. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* 52:276–284.
- Hertzman C, Wiens M, Snow B, Kelly S, Calne D. 1994. A case-control study of Parkinson's disease in a horticultural region of British Columbia. *Mov Disord* 9:69–75.
- Hu G, Antikainen R, Jousilahti P, Kivipelto M, Tuomilehto J. 2008. Total cholesterol and the risk of Parkinson disease. *Neurology* 70(21):1972–1979.
- Hu G, Jousilahti P, Nissinen A, Antikainen R, Kivipelto M, Tuomilehto J. 2006. Body mass index and the risk of Parkinson disease. *Neurology* 67(11):1955–1959.
- Kamel F, Tanner C, Umbach D, Hoppin J, Alavanja M, Blair A, et al. 2007. Pesticide exposure and self-reported Parkinson's disease in the agricultural health study. *Am J Epidemiol* 165(4):364–374.
- Kuopio AM, Marttila RJ, Helenius H, Rinne UK. 1999. Environmental risk factors in Parkinson's disease. *Mov Disord* 14(6):928–939.
- Langston JW. 2006. The Parkinson's complex: parkinsonism is just the tip of the iceberg. *Ann Neurol* 59(4):591–596.
- Langston JW, Ballard P, Tetrd JW, Irwin I. 1983. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 219(4587):979–980.
- Lee SJ. 2003. Alpha-synuclein aggregation: a link between mitochondrial defects and Parkinson's disease? *Antioxid Redox Signal* 5(3):337–348.
- Logroscino G, Sesso HD, Paffenbarger RS Jr, Lee IM. 2007. Body mass index and risk of Parkinson's disease: a prospective cohort study. *Am J Epidemiol* 166(10):1186–1190.
- Marras C, Tanner CM. 2002. The epidemiology of Parkinson's disease. In: *Movement Disorders Neurologic Principles and Practice* (Watts RL, Koller WC, eds). New York:McGraw-Hill, 177–196.
- Marsh GM, Gula MJ. 2006. Employment as a welder and Parkinson disease among heavy equipment manufacturing workers. *J Occup Environ Med* 48(10):1031–1046.
- Mayeux R, Marder K, Cote LJ, Denaro J, Hemenegildo N, Mejia H, et al. 1995. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988–1993. *Am J Epidemiol* 142(8):820–827.
- Mergler D, Huel G, Iregren A, Belanger S, Baldwin M, Tardif R, et al. 1994. Nervous system dysfunction among workers with long-term exposure to manganese. *Environ Res* 64:151–180.
- Park M, Ross GW, Petrovitch H, White LR, Masaki KH, Nelson JS, et al. 2005. Consumption of milk and calcium in midlife and the future risk of Parkinson disease. *Neurology* 64(6):1047–1051.
- Pfeiffer RF. 1998. Gastrointestinal dysfunction in Parkinson's disease. *Clin Neurosci* 5(2):136–146.
- Popat RA, Van Den Eeden SK, Tanner CM, McGuire V, Bernstein AL, Bloch DA, et al. 2005. Effect of reproductive factors and postmenopausal hormone use on the risk of Parkinson disease. *Neurology* 65(3):383–390.
- Powers KM, Kay DM, Factor SA, Zabetian CP, Higgins DS, Samii A, et al. 2008a. Combined effects of smoking, coffee, and NSAIDs on Parkinson's disease risk. *Mov Disord* 23(1):88–95.
- Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr, Swanson PD, Checkoway H. 2008b. Dietary fats, cholesterol and iron as risk factors for Parkinson's disease. *Parkinsonism Relat Disord*; doi:10.1016/j.parkrel.2008.03.002 [Online 18 April 2008].
- Prince MM, Hein MJ, Ruder AM, Waters MA, Laber PA, Whelan EA. 2006. Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors, 1940–1998. *Environ Health* 22:5:13.
- Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. 2001. Environmental risk factors and Parkinson's disease: a meta-analysis. *Environ Res* 86(2):122–127.
- Purisai MG, McCormack AL, Langston JW, Johnston LC, Di Monte DA. 2005. Alpha-synuclein expression in the substantia nigra of MPTP-lesioned non-human primates. *Neurobiol Dis* 20(3):898–906.
- Ritz B, Ascherio A, Checkoway H, Marder KS, Nelson LM, Rocca WA, et al. 2007. Pooled analysis of tobacco use and risk of Parkinson disease. *Arch Neurol* 64(7):990–997.
- Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH, et al. 2000. Association of coffee and caffeine intake with the risk of Parkinson disease. *JAMA* 283(20):2674–2679.
- Ross GW, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K, et al. 2008. Association of olfactory dysfunction with risk for future Parkinson's disease. *Ann Neurol* 63(2):167–173.
- Santamaria AB, Cushing CA, Antonini JM, Finley BL, Mowat FS. 2007. State-of-the-science review: does manganese exposure during welding pose a neurological risk? *J Toxicol Environ Health B Crit Rev* 10(6):417–465.
- Simon KC, Chen H, Schwarzschild M, Ascherio A. 2007. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology* 69(17):1688–1695.
- Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, et al. 2003. Alpha-synuclein locus triplication causes Parkinson's disease. *Science* 302(5646):841.
- Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M. 1998. Alpha-synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proc Natl Acad Sci USA* 95(11):6469–6473.
- Steenland K, Hein MJ, Cassinelli RT 2nd, Prince MM, Nilsen NB, Whelan EA, et al. 2006. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohort. *Epidemiology* 17(1):8–13.
- Stern MB, Doty RL, Dotti M, Corcoran P, Crawford D, McKeown DA. 1994. Olfactory function in Parkinson's disease subtypes. *Neurology* 44(2):266–268.
- Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, et al. 1999. Parkinson disease in twins: an etiologic study. *JAMA* 281(4):341–346.

- Thacker EL, Chen H, Patel AV, McCullough ML, Calle EE, Thun MJ. 2008. Recreational physical activity and risk of Parkinson's disease. *Mov Disord* 23(1):69–74.
- Thiruchelvam M, Richfield E, Baggs R, Tank A, Cory-Slechta D. 2000. The nigrostriatal dopaminergic system as a preferential target of repeated exposures to combined paraquat and maneb: implications for Parkinson's disease. *J Neurosci* 20(24):9207–9214.
- Tuchsen F, Jensen AA. 2000. Agricultural work and the risk of Parkinson's disease in Denmark, 1981–1993. *Scand J Work Environ Health* 26:359–362.
- Uversky V. 2004. Neurotoxicant-induced animal models of Parkinson's disease: understanding the role of rotenone, maneb and paraquat in neurodegeneration. *Cell Tissue Res* 318(1):225–241.
- Uversky V, Li J, Fink A. 2001. Pesticides directly accelerate the rate of alpha-synuclein fibril formation: a possible factor in Parkinson's disease. *FEBS Lett* 500(3):105–108.
- Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, et al. 2003. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol* 157:1015–1022.
- Vila M, Vukosavic S, Jackson-Lewis V, Neystat M, Jakowec M, Przedborski S. 2000. Alpha-synuclein up-regulation in substantia nigra dopaminergic neurons following administration of the parkinsonian toxin MPTP. *J Neurochem* 74(2):721–729.
- Wahner AD, Bronstein JM, Bordelon YM, Ritz B. 2007. Nonsteroidal anti-inflammatory drugs may protect against Parkinson disease. *Neurology* 69(19):1836–1842.
- Wahner AD, Bronstein JM, Bordelon YM, Ritz B. 2008. Statin use and the risk of Parkinson disease. *Neurology* 70(16 pt 2):1418–1422.
- Warner T, Schapira A. 2003. Genetic and environmental factors in the cause of Parkinson's disease. *Ann Neurol* 53(suppl 3):S16–S25.
- Weisskopf M, O'Reilly E, Chen H, Schwarzschild M, Ascherio A. 2007. Plasma urate and risk of Parkinson's disease. *Am J Epidemiol* 166(5):561–567.
- Wirdefeldt K, Gatz M, Schalling M, Pedersen NL. 2004. No evidence for heritability of Parkinson disease in Swedish twins. *Neurology* 63(2):305–311.
- Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J. 2004. Are men at greater risk for Parkinson's disease than women? *J Neurol Neurosurg Psychiatry* 75(4):637–639.
- Zhang SM, Hernán MA, Chen H, Spiegelman D, Willett WC, Ascherio A. 2002. Intakes of vitamins E and C, carotenoids, vitamin supplements, and PD risk. *Neurology* 59(8):1161–1169.
- Zhang ZX, Anderson DW, Huang JB, Li H, Hong X, Wei J. 2003. Prevalence of Parkinson's disease and related disorders in the elderly population of greater Beijing, China. *Mov Disord* 18(7):764–772.
- Zhang ZX, Román GC. 1993. Worldwide occurrence of Parkinson's disease: an updated review. *Neuroepidemiology* 12(4):195–208.